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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,599	PASTAN ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *19-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *19-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on March 4, 2005, are acknowledged and have been entered. Claims 19, 21-23, 30, 32 have been amended. An action on the RCE follows.

2 Claims 19-32 are pending and currently under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC 112

4. If remain rejected under 35 USC 112, first paragraph and claim 26 is rejected under 35 USC 112, first paragraph essentially for the reasons previously set forth in the action mailed August 25, 2004, Section 4, pages 2-5.

Applicant argues that the claims as currently constituted are not drawn to vaccines, but rather are drawn to isolated proteins and peptides. Further, the claimed proteins and peptides are useful, for example, to raise antibodies which are useful for detecting the presence of mesothelin and the action neither alleges nor shows that raising antibodies by the claimed proteins and peptides is not an appropriate utility or is not enabled. Applicant reminds Examiner that a composition requires only one utility to be patentable and that it only need be enabled for that utility.

The argument has been considered but has not been found persuasive. Examiner reminds Applicant that the rejection in Section 4, pages 2-5 is not a utility rejection, but rather an enablement rejection. As previously set forth, the

claimed invention reads on anti-cancer vaccines and Applicant's previous amendment to the claims, to delete the term "vaccine" does not alter that fact. Although no longer specifically recited in the claims, the vaccine limitation is inferred by the claim language because the claims read on the use of the claimed peptides and proteins as immunogens (which reads specifically on *in vivo* administration) in patients with mesothelioma-or ovarian cancer-cells expressing mesothelin, given the understanding in the art that T-cells generated by vaccines will recognize, *ex vivo* the immunogen use to produce them *in vivo*, as well as the understanding in the art that administration of peptide vaccines result in not only a humoral but also a cellular immune response wherein both antibodies and T-cells are produced. Further, given the clear teachings of the specification that the antibodies raised by the immunogens of the invention would be useful in inhibiting the spread or implantation of ovarian cancer cells in the peritoneal wall, given the teaching in the specification that the administration of peptides is well known for treatment of a variety of diseases, given the teaching that one of skill is able to extrapolate the information available for use of peptides to treat diseases associated with mesothelin with mesothelin peptides, given the specific teaching in the specification of vaccines comprising SEQ ID NO:2 or fragments thereof for the prevention of and inhibition of tumors, it is reasonable to infer from the claims as currently constituted that the claims read on anti-cancer vaccines for the treatment of mesothelioma-or ovarian cancer cells and that these limitations are encompassed by the claims and for the reasons of record, the claims are not enabled. Finally, although Applicant suggest that the claimed invention, SEQ ID NO:2 and variants thereof, is useful for the production of antibodies to be used for detecting the presence of mesothelin in a biological sample and for targeting cytotoxins to cells

expressing mesothelin, given that the only useful function disclosed in the specification is apparently for the diagnosis and treatment of cancer, one would not know how to use the claimed invention if it were not used for the methods contemplated in the specification. If indeed there is no differential expression of SEQ ID NO:2 in cancer and normal tissues, one would reasonably wonder why one would make antibodies to target cytotoxins to normal tissues and what one would one use information about the detection of SEQ ID NO:2 in a biological sample for except, perhaps, for experimental reasons. Further, Applicant appears to admit on the record that the specific function of SEQ ID NO:2 is unknown (see response, page 9, first full paragraph). Given this teaching, one would clearly not know how to use the claimed invention, or antibodies raised to said invention. The arguments have been considered but have not been found persuasive and the rejeciton is maintained.

5. If Applicant were able to overcome the rejection set forth above, Claims 20-25, 27-32 would remain rejected under 35 USC 112, first paragraph essentially for the reasons previously set forth in the action mailed August 25, 2004, Section 5, pages 5-18.

Applicant argues points to the MPEP that claims are permitted to encompass non-working embodiments, so long as there is a test by which the person of skill can readily determine whether or not a composition is within the scope of the claims without undue experimentation and points to *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577,224 USPQ 409, 414 (Fed. Cir. 1984). The argument has been considered but has not been found persuasive because the issue raised here is not non-working embodiments, but rather that neither the specification nor the claims of record teach how to make the claimed

invention so that it will function as broadly claimed. The specification does not point to critical regions of the polypeptide that must be conserved in order to produce the inferred anti-cancer vaccine, provides no guidance or information drawn to which regions of the claimed SEQ ID NO:2 are exposed on the outside of the undefined antigen, where the polypeptide is glycosylated, provides no information as to which epitopes are linear or 3-dimensional in the claimed variants of SEQ ID NO:2 wherein these variants are useful as the inferred anti-cancer vaccine. The arguments have been considered but have not been found persuasive and the rejeciton is maintained.

6. Claims 20-25 and 27-32 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed August 25, 2004, Section 8, pages 19-25.

Applicant argues that the findings in Lilly and Enzo do not relate to proteins and peptides. The courts recognize the degeneracy of the genetic code while amino acids constituting the sequence of proteins is not degenerate. In any case, the claims recite proteins and peptides have a defined degree of sequence identity to SEQ ID NO:2 which retain defined functions and such claims are routinely accepted by the Office as complying with the statutory requisities for patenting, including written description and the Action has presented no reason why the same treatment is not appropriate in this case.

The argument has been considered and has not been found persuasive because the courts have consistenty found that the fact pattern in Lilly and Enzo can be extrapolated to molecular products other than polynucleotides and that the standards defined by the court decisions are applicable to both polynucleotides and polypeptides. The degeneracy or lack thereof of the genetic code or protein

sequences is not the issue raised here. The issue raised here that the specification as originally filed does not structurally describe a representative number of the genus claimed, does not describe structural features common to the members of the genus which features constitute a substantial portion of the genus, does not disclose functional characteristics coupled with a known or disclosed correlation between function and structure. The argument has been considered but has not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC 102

7. Claims 19-25 and 27-32 remain rejected under 35 USC 102(b) and claim 26 will also be rejected under 35 USC 102(b) for the reasons previously set forth in the action mailed August 25, 2004, Section 12, pages 26-27.

Applicant argues that Figure 3 of the Chang paper does not show an isolated 40 kDa CAK1 protein because a Western blot is designed to reveal the protein bound by the probing antibody without revealing the presence of any number of othe proteins that may also be present but which are not bound by the antibody used. Thus while Figure 3 shows the presence of the CAK1 antigen, it does not and was not intended to show the presence of the many other membrane proteins and glycoproteins that were released by the PI-PLC digestion.

The argument has been considered but has not been found persuasive because the specification clearly teaches that the terms "isolated," "purified," or "biologically pure" refer to material which is substantially or essentially free from components which normally accompany it as found in its native state. It is noted that the specification does not define the terms substantially or essentially free and one of ordinary skill would immediately understand that the protein isolated in a western blot is substantially and essentially free of components which normally

accompany it as found in its native state given that the claimed protein is substantially or essentially free of nucleic acid molecules which normally accompany it in its native state. The arguments have been considered but have not been found persuasive and the rejection is maintained. It is noted that Applicant does not argue that the isolated protein of Chang et al is not the same as the claimed invention, does not disclose whether SEQ ID NO:2 is the 40 kDA protein or the 69 kDa protein.

New Grounds of Rejection

Claim Rejections - 35 USC 112

8. If Applicant were able to overcome the rejection of Claims 20-25, 27-32 for the reasons set forth above under 35 USC 112, first paragraph, claims 20-25, 27-32 would still be rejected under 35 USC 112, first paragraph because the specification, while enabling for an isolated protein comprising SEQ ID NO:2, does not reasonably provide enablement for an isolated protein having at least 85% identity to SEQ ID NO:2, an isolated peptide having 90% sequence identity over a comparison window of about 10-20 amino acid residues to SEQ ID NO:2, a composition comprising said isolated protein, a composition comprising a peptide comprising at least 10 contiguous amino acids of mesothelin, SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification teaches that it would be useful to have antibodies that recognize differentiation antigens on solid tumors but that only a small number of these are available (p. 1, lines 34-40) and further teaches that an antibody previously isolated reacts with many ovarian cancers and mesotheliomas as well as

normal mesothelial cells as well as some cells in the trachea (p. 2, lines20-25), The antigen recognized by MabK1 appears to be a differentiation antigen present on mesothelium and is expressed on cancers derived from mesothelium as well as on most ovarian cancers. The specification suggests that immunotherapy directed at the CAK1 antigen (mesothelin/SEQ ID NO:2) should take into account the potential risk of damaging normal mesothelial cells and perhaps cells of the trachea (p. 2, lines 27-37). The antigen has been characterized using the ovarian cancer cell line OVCAR-3 as well as HeLa cells and is a 40 kD glycoprotein attached to the cell surface by phosphatidylinositol. The 40kD glycoprotein is processed from a preprotein of 69 kD (p. 3, lines 22-24). The specification hypothesizes that antibodies to mesothelin would be useful in inhibiting the spread or implantation of ovarian cancer cells that accumulate on the peritoneal wall and without intending to be bound by theory, the instant inventors believe that the antigen is likely responsible for the adhesion and implantation of ovarian carcinoma cells since mesothelin transfectants are more slowly removed from culture dishes than non-transfected cells (p. 10, lines 20-32). Mesothelin is very abundant in normal mesothelial cells from which malignant mesotheliomas and ovarian cystadenocarcinomas are derived and the specification hypothesizes that mesothelin likely has a role in the aggressive spread of these tumors throughout the peritoneal or thoracic cavity (p. 11, lines 4-9). The specification suggests that the detection of mesothelin is useful as an indicator of the presence of tumor cells (p. 11, lines 17-18) and states that the administration of peptides is well known for a variety of diseases and that one of skill is able to extrapolate the information available for use of peptides to treat diseases associated with mesothelin with mesothelin peptides or antibodies to mesothelin (para bridging pages 37-38). The

specification further teaches vaccines comprising SEQ ID NO:2 or fragments thereof for the prevention of and inhibition of the growth of tumors bearing mesothelin (p. 44, lines 10-15). The cloned cDNA encoding SEQ ID NO:2 was transfected into and expressed in mammalian cells (p. 51). The specification states that SEQ ID NO:1 is found on mesothelium, mesotheliomas, ovarian cancers and some squamous cell carcinomas (p. 55, Section C). Finally the specification states that the amino terminal fragment has recently been detected in the medium of OVCAR-3 cells (p. 56).

One cannot extrapolate the teaching of the specification to the scope of the claims because the claims as written are drawn to variants of SEQ ID NO:2 with 95 undefined alterations of the 628 amino acid residues of SEQ ID NO:2 as well as undefined variants which comprise 9 or 10 amino acids of SEQ ID NO:2 and neither the specification nor the art of record define which amino acid residues are critical to the raising of antibodies that are specific for SEQ ID NO:2 or which will be recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin. As drawn to antibodies, Bowie, of record, teaches that an amino acid sequence encodes a message that determines the shape of a protein and determines the ability of said protein to fold into unique three-dimensional structures that allows them to function. Bowie further teaches that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (p. 1306, cols 1 and 2). Clearly, the three dimension structure of a protein is critical to the production of antibodies given the teaching of Herbert et al (The Dictionary of Immunology, Academic Press, 3rd Edition, London, 1985, pges 58-59). Herbert et al who specifically teach that an epitope is the region on an

antigen molecule to which antibody specifically binds. B cell epitopes on protein antigens are of variable size comprising up to about 20 amino acids. Antibodies bind in a more or less exact three dimensional fit with an epitope. This may be formed from residues on different regions of a protein antigen molecule which, in the native state, are closely apposed due to protein folding. Thus the three-dimensional structure of the protein molecule may be essential for antibody binding. (p. 58). However, neither the specification nor the art of record provide teachings that provide information about the residues critical for epitopes required for the establishment of an immune response that will produce antibodies that recognize full-length mesothelin. This information appears to be critical because the art recognizes (see Bowie above) that it is the protein sequence that determines the three dimensional shape of a protein and Herbert et al specifically state that antibodies bind in a more or less exact three dimensional fit and suggests that the three-dimensional structure of the protein molecule may be essential for antibody binding. Thus, in the absence of guidance in the specification, the effects of the undefined alteration of 95 of the 628 amino acids of SEQ ID NO:2 on the three-dimensional structure of the claimed isolated protein, and thus the antibodies that will be produced from and bind to that structure, cannot be predicted and one could not determine how to make the claimed invention or predict which of the whole universe of broadly claimed polypeptides would function as claimed with a reasonable expectation of success.

Further, it is noted that a peptide is defined as a compound formed by hydrolytic cleavage of peptides and containing two or more amino acids in Taber's Cyclopedic Medical Dictionary, FA Davis, Philadelphia, 16th Ed., 1985, page 1354. Given the art recognized definition, pending claim are drawn to peptides

having 90% identity over a comparison window of about 10-20 amino acids, comprising 10 contiguous amino acids of SEQ ID NO:2 read on polypeptides of undefined length and constitution wherein the three dimensional structure of the 9 or 10 amino acids of SEQ ID NO:2 comprised within the polypeptides are unknown. Neither the art nor the specification as originally filed provides guidance on how to determine which 10-20 amino acids with 90% identity. 10 contiguous amino acids will be capable of, when used as an immunogen, raising antibodies which bind specifically to SEQ ID NO:2. In particular, Roitt et al, of record teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the teaching of Holmes, of record who teaches that rabbits were immunized with synthetic peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the antibodies exhibited binding to the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability' (p. 513, col 1). Furthermore, the specification does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. Given this teaching, even if the peptides

claimed consisted of amino acid residues that were 100% identical to portions of SEQ ID NO:2 having 100% sequence identity over a comparison window of 10-20 amino acid residues to SEQ ID NO:2 it would not be possible to determine with any predictability whether the antibodies produced from such a fragment that is specific for SEQ ID NO:2 actually bind to SEQ ID NO: 2, in the absence of guidance from the specification.

Further, there is no teaching in the specification of whether or not the epitopes are linear or comprise 3-dimensional structures. In particular, Greenspan et al, of record teaches that defining epitopes is not as easy as it seems. Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column).

As drawn to recognition of the protein by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin, Herbert et al, Supra, teaches that T-cells recognize peptide fragments which have been processed by an accessory cell and presented in the cleft of a class I MHC antigen or a class II MHC antigen and that a continuous primary sequence is necessary for T cell recognition (p. 58). It is obvious that T cell epitopes and antibody epitopes are not the same. However, the issues drawn to the lack of guidance in the specification as to critical residues and polypeptide fragments required for T cell binding are relevant to this limitation as well. Further, even if the peptides claimed were 100% identical to specific portions of SEQ ID NO:2 it would not be possible to determine with any predictability which of the portions of SEQ ID NO:2 comprise T cell epitopes that would be recognized by T-cells from cancer patients. Further,

Chaux et al, of record teach that some CTLs have an affinity that is too low for the recognition of cells that have processed the antigen, which is different from the *in vitro* conditions in which the synthetic peptides are in high number when incubated with the cells (p.541, second column, second paragraph). Given the above, even if a peptide was recognized by T-cells *in vitro* from patients with mesothelioma or ovarian cancer cells expressing mesothelin, it could not be predicted that the T-cells would recognize these peptides *in vivo* and if not recognized *in vivo*, it is clear that one would not know how to use the claimed peptides. Similarly Sherman et al, of record teach that self-tolerance may eliminate T cells that are capable of recognizing T-cell epitopes with high avidity . Smith, of record teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limit the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specific antigen in the necessary MHC context (p.484). It is noted that these references remain relevant to the instant rejection even though Applicant has amended the claims to delete reference to a vaccine for the inhibition or of mesotheliomas or ovarian tumors. The claims as they are drawn to peptides with T-cell epitopes still read on a vaccine since the only contemplated use for peptides as drawn to T-cell's is for vaccination for the inhibition of mesothelioma or ovarian tumors. Given the above, one would not know how to make or use the claimed peptides even if they could be recognized *in vitro* by T-cells from cancer patients. Again, Boon, of record teaches that for active immunization in human patients we have to stimulate immune

defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence, as set forth above, suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). Thus based on the teaching in the art and in the specification, one cannot predict that an adequate *in vivo* T cell response useful for immunotherapy, as contemplated, could be induced by the peptides of the invention in having tumor burden.

Finally, as drawn to peptide tumor vaccines for the induction of a T-cell response, Kirkin et al, of record review several melanoma-associated antigens, including NY-ESO1, and conclude that initiation of a strong immune response *in vivo* is an extremely rare event (p.674, first column, last paragraph). Kirkin et al teach that for some antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Kirkin et al teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response *in vivo*, only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (p.666, second column, second paragraph, last 6 lines). Further, even this peptide EVDPIGHLY of MAGE-A3 produces a very low level of CTL response which is detectable only by a very sensitive method, as taught by Chaux et al, of record. Although the

peptides used were peptides with 100% identity NY-ESO1, wherein sophisticated techniques were used to predict which sequences might effective to produce T-cells for the treatment of disease, the immune response to those peptides was not effective. Thus, it would not be expected that the claimed variant proteins/peptides, in the absence of further guidance from the specification, would function as claimed or as contemplated given that there is no teaching of residues critical to the claimed function.

The specification provides no guidance or working examples which would provide guidance to one skilled in the art as to which amino acids or polypeptide fragments are critical to the production of antibodies which recognize full length SEQ ID NO:2 or could be recognized by T-cells from patients with mesothelioma- or ovarian cancer-cells expressing mesothelin and no evidence has been provided which would allow one of skill in the art to predict which of the broadly claimed polypeptide variants would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Applicant's arguments submitted in the paper filed December 15, 2004 are relevant to the instant rejection.

Applicant argues that the recitation of proteins and peptides which have a defined degree of sequence identity to a particular novel protein and which retain a particular function is a common claim format.

The argument has been considered but has not been found persuasive because although the claim language may be conventionally used, Examiner reminds Applicant that each case is examined on its own merits. Given that the specification provides no teaching as to critical amino acid residues required for

the invention to funciton as claimed, the claims are not enabled for the reasons set forth above.

Applicant argues that to determine whether or not antibodies raised by any particular protein or peptide actually bind to SEQ ID NO:2 can be easily accomplished by standard immunoassays such as ELISAs. If Examiner chooses to maintain this portion of the rejection, Applicants respectfully request that the Examiner explain why these standard techniques, in use for decades, would not be successful in determining whether the antibodies raised would actually bind to SEQ ID NO:2.

The argument has been considered but has not been found persuasive because the standard for enablement under 35 USC 112, first paragraph is not whether the specification teaches how to screen for a particular moiety, but rather, how to make and use the claimed invention. Again as set forth above, the specification provides no guidance or information drawn to which regions of the claimed SEQ ID NO:2 are exposed on the outside of the undefined antigen, where the polypeptide is glycosylated, provides no information as to which residues are critical for the invention to function as broady claimed.

Applicant reminds the Examiner that the tertiary structure of a molecule is determined by its primary structure and therefore the tertiary structure of SEQ ID NO:2 is known. Applicant argues that although it is possible that proteins with 90% sequence identity to SEQ ID NO:2 will have a different conformation and therefore different conformational epitopes, it is unlikely that they will not have portions that do not have linear or conformational epitopes that will raise antibodies that also bind to SEQ ID NO:2 and if they do not, they are not within the scope of the claims. Applicant reminds Examiner that claims are permitted to

encompass inoperable embodiments so long as the practitioner can determine whether or not the embodiment is operable with no more effort than is normally used in the art and the practitioner can test any protein with tests commonly conducted in the art.

The argument has been considered but has not been found persuasive. It is noted that the claims are not drawn to 90% identity, but rather are drawn to proteins having, that is comprising, 85% identity to SEQ ID NO:2, peptides comprising 90% identity over a comparison window of about 10-20 amino acid residues, an isolated peptide comprising at least 10 contiguous amino acids of SEQ ID NO:2. As set forth previously and above, the specification provides no guidance or information drawn to which residues or regions of the claimed SEQ ID NO:2 are critical to the claimed invention, which are exposed on the outside of the undefined antigen, where the polypeptide is glycosylated, provides no information as to which epitopes are linear or 3-dimensional in the claimed variants of SEQ ID NO:2. Although it is possible that through serendipity, a set of the claimed variants might produce a subset of antibodies that bind to SEQ ID NO:2, given that no information has been provided drawn to critical amino acid residues and regions required for the invention to function as claimed, it appears that the skilled artisan is left only with random experimentation to make the claimed invention and random experimentation is undue. The issue raised here is not that claims are not permitted to encompass inoperable embodiments, but rather that the teachings of the specification do not enable the practitioner to predictably determine which of the whole universe of molecules claimed will function as claimed with a reasonable expectation of success.

Applicant argues that peptides that are fragments of SEQ ID NO:2 or that share 90% identity with such fragments may well only relate to linear epitopes, not conformational epitopes and that linear epitopes are useful for example to bind to denatured protein of SEQ ID NO:2 in SDS-PAGE and Western blots and Applicant is unaware of any requirement of the patent law that the claimed peptides have to also raise antibodies against conformational epitopes.

The argument has been considered but has not been found persuasive because neither the specification nor the art of record provides guidance as to the critical residues or regions of SEQ ID NO:2 required in order to practice the invention as broadly claimed. Although Applicant hypothesizes that fragments of SEQ ID NO:2 or that share 90% identity with such fragments may well only relate to linear epitopes, this hypothesis is not convincing given the lack of guidance in the specification, the lack of working examples in the specification that would provide guidance to one of ordinary skill that would enable the practitioner to make variants of SEQ ID NO:2 as claimed that will predictably , when used ass an immunogen, raise antibodies which recognize full-length mesothelin, SEQ ID NO:2 or be recognized by T-cells from patients.

Applicant further argues that Bowie, is not relevant to the instant rejection since this references relate to the biological activity of proteins. The argument has been considered but has not been found persuasive because Bowie is cited only to demonstrate the critical nexus between defined amino acid sequence and three-dimensional structure. Examiner goes on to provide a nexus between three-dimensional structure and antibody binding and generation. Applicant's argument appears to be moot.

Applicant further argues whether or not antibodies raised by any particular protein or peptide actually binds to SEQ ID NO:2 can easily be accomplished by standard immunoassays such as ELISAs and Examiner is asked to explain why these standard techniques would not be succesful in determining whether the antibodies raised would "actually bind to SEQ ID NO:2" The argument has been considered but has not been found persuasive. As set forth above, the enablement requirement is not drawn to how to screen, but rather is drawn to how to make and use and for the reasons set forth above, the invention is not enabled as broadly claimed.

Applicant further argues that it is unlikely that proteins with 90% identity to SEQ ID NO:2 will have a different conformation than SEQ ID NO;2 and therefore different conformational epitopes. The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited in the claims as currently constituted.

Applicant further argues that only 4 glycosylation points are found on SEQ ID NO:2 and the action presents no evidence to show that the presence of a few carbohydrates would prevent the generation of antibodies to other portion of the protein and further argues that the claims are permitted to encompass inoperable embodiments. The argument has been considered but has not been found persuasive because the issue raised here is not drawn only to the glycosylation sites but is drawn to the inadequacy of the teaching of the specification drawn to critical residues and regions of SEQ ID NO:2 that would enable one to predictably make the claimed invention with a reasonable expectation of success.

Applicant further argues that Kirkin and Chaux are not relevant to the claims under examination since Kirkin is concerned exclusively with melanoma-

associated antigens and Chaux concerns the development of an extremely sensitive immunoassay for detecting CTL precursors. The argument has been considered but has not been found persuasive because, as noted previously and above, these references remain relevant to the instant rejection even though Applicant has amended the claims to delete reference to a vaccine for the inhibition of mesotheliomas or ovarian tumors. The claims as they are drawn to peptides with T-cell epitopes still read on a vaccine since the only contemplated use for peptides as drawn to T-cell's is for vaccination for the inhibition of mesothelioma or ovarian tumors. Further, these references clearly delineate the state of the art at the time the invention was made wherein it was commonly understood that peptide vaccines were not effective for treatment the reasons of record.

Applicant further argues that Smith does not recite at page 484 that tumors progressively lose MHC representation at the sruvace of the cell and Examiner is requested to clarify the reference and Applicants respectfully note that the present claims are drawn to compositions, not methods and even if tumors lose MHC represenetation over time, that does not diminish the value of raising a T cell response early in treatment and nothing in the patent statute requires that a composition be useful throughout the entire course of a disease. The argument has been considered but has not been found persuasive because although Applicant asks for clarification as to where the information is found in the Smith article, Applicant does not argue that the statement in the action is not true. Further, for the reasons previously set forth, one would not know how to use the claimed invention.

Applicant further argues that pulsing or loading dendritic cells with antigen to primed T cells was known in the art at the time the invention was made and thus

techniques already existed to break self-tolerance adequately to enable the invention as claimed. The argument has been considered but has not been found persuasive because the claims are not drawn to pulsed or loaded dendritic cells.

Applicant cites Jager et alSillman et al, Mayordomo et al, Paglia et al, Porgador et al and argues that adjuvants were known in the art in 1998 and that adjuvants were used to increase the robustness of the immune response to cancer antigens. Thus it was known in the art that the immune response could be augmented and the specification presents lists of exemplar adjuvants. The arguments have been considered but have not been found persuasive because the specification does not provide guidance or teachings that would enable the practitioner to practice the claimed invention with a reasonable expectation of success for the reasons set forth previously and above.

Applicant argues that the vaccine aspect of the invention is not the on contemplated use for the peptides of the invention. As pointed out above, it was known in the art at the time of filing that dendritic cells could be pulsed or loaded with tumor antigen peptides in vitro and that such dendritic cells could be used to develop specific T-cell responses *in vivo*. The argument has been noted but has not been found persuasive since dendritic cell pulsing is still drawn to the use of the peptides for a vaccine. Further, it is noted that Applicant does not point to the specification to support the contention that other uses of the invention were contemplated by the inventors at the time the application was filed. Although Applicant states that it is irrelevant that this use may not have been set forth in the specification in so many words, the well established rule is that the specification need not teach that which is well known in the art and cites *In re Buchner*. A

review of *In re Buchner* reveals that Applicant is mischaracterizing the findings of the courts, which in fact are drawn to the test of enablement, that is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. The court found that in terms of enablement, a patent need not teach, and preferably omits, what is well known in the art. This case is not drawn to the lack of contemplation of a specific embodiment. The argument has been considered but has not been found persuasive.

Applicant argues that Boon does not teach what would happen if the tumor rejection antigens were administered to a patient with a less advanced cancer and consequently a low tumor burden,Boon does not indicate that there is no population of patients of mesothelin expressing cancers that would have an increased immune response to the cancer as a result of adminstration of the peptides of the invention. The argument has been considered but has not been found persuasive since given the information known in the art it is clear that it is not more likely than not that the claimed peptides could be successfully used as contemplated in the specification and inferred in the claims.

Applicant argues that there is no requirement that the proteins and peptides of the invention induce an immune response in every patient and appears to be arguing once again that non-working embodiments are permitted. The argument has been considered previously and is not found persuasive for the reasons set forth above.

Applicant argues that although Boon suggests that a cancer antigen may not be expressed on all cells of a cancer and therefore might not be therapeutically useful, it is useful to the practitioner and to the patient if disease progression is

reduced by affording some response to those cells of the tumor that do express the antigen and thus this issue is irrelevant to the enablement of the claims. The argument has been considered but has not been found persuasive because Boon's teachings reflect the state of the art wherein it was known that the efficacy antigen-specific therapy is dependent upon abundance of antigen presented by the tumor. Applicant's suggestion that tumor progression can be reduced in the absence of sufficient abundance of the antigen target is repugnant to the art and goes against the teachings of those of skill.

Applicant states that although the Action indicates that Boon states that there is inconsistent antigen expression and prsentation by tumor cells, even if activated CTLS are significantly increased, Applicant was unable to locate the passage in Boon where this assertion is made. It is noted however, that although Applicant was unable to locate the passage in Boon, Applicant did not argue that the statements made by Examiner are incorrect.

Applicant argues that Kirkin is irrelevant because the teachings are not drawn to mesothlin-expressing tumors but are drawn to melanoma-associated antigens and therefore are not relevant to the instant invention. Further, if the teachings of Kirkin were drawn to peptides with anti-cancer effects in general, Kirkin might be applicable. The argument has been considered but has not been found persuasive since the mechanisms discussed in Kirkin reflect the state of the art and are drawn specifically to the immune system response which as Applicant must be aware is a general response to foreign moieties administered to a patient. Given the findings of Kirkin it is clear that the art is unpredictable for this type of therapy for peptides with 100% identity to the tumor antigen targeted. Clearly it is

much more unpredictable for peptides with less than 100% identity to the tumor antigen targeted for the reasons set forth above.

Applicant argues that Examiner's finding of the requirement for undue experimentation to practice the claimed invention based on the unpredictability of antigen expression taught by Boon, the lack of induction of a strong immunogenic effect taught by Kirkin, the teachings of Bowie that alterations in amino acid sequence could affect the ability to stimulate T cell responses to SEQ ID NO:2 is not supported by the references. In particular, Applicant argues that (a) he could not locate the specific passage referred to in Boon, (b) Kirkin has been shown to be not relevant for the reasons set forth above, (c) the teachings of Bowie are not apposite to the claims under Examination. The arguments have been considered but have not been found persuasive because (a') although Applicant is unable to locate the cited passage, Applicant has not suggested that the information drawn to antigen presentation and abundance is not correct, (b') Kirkin is relevant for the reasons set forth above, (c') given the new grounds of rejection set forth above, Bowie is relevant to the instant rejection. Thus, close examination demonstrates that the references cited by the action support the Examiner's position.

Applicant argues that rejection of the claims on grounds that vaccines are not enable inappropriately imports into the claims a recitation that is not present. The argument has been considered but has not been found persuasive for the reasons set forth previously and above.

Applicant argues that the Action's argument that the peptide vaccines are unpredictable rests on combining references that as shown in the preceding section are not analogous to or relevant to the claims under examination. The argument

has been considered but has not been found persuasive for the reasons set forth above.

Applicant argues that the Action's argument ignores the loading of peptides onto dendritic cells, a technique that was known prior to the priority date. The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited in the claims as currently constituted, the claims are not drawn to loaded dendritic cells. Further, Applicant is arguing an embodiment not contemplated in the specification or claims as originally filed.

The arguments have been carefully considered but have not been found persuasive and the rejection above under 35 USC 112, first paragraph, stands.

9. Claims 20, 23-26 are rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitation of "at least 85% sequence identity to SEQ ID NO:2" recited in claims 20 and 23 has no clear support in the specification and the claims as originally filed. Applicant points to page 6, lines 19-25 for support for the newly added limitation in the paper submitted December 15, 2004 and specifically cites the specification wherein the specification teaches that a polypeptide has substantial identity to another when it **has** (emphasis added) 85% sequence identity to a reference polypeptide. A review of page 6, lines 19-25 reveals support for "at least 70% sequence identity.....or preferably 80%, or more preferably 85% sequence identity to the reference sequence. Thus, Applicant is indeed correct, the specification supports the embodiment of a sequence that has 85% sequence identity to the reference polypeptide. However, the modifier "at least" is drawn only to the 70% sequence identity. Thus, Applicants suggestion of support, although carefully considered, is not found persuasive. The subject matter claimed

in claims 20, 23-26 broadens the scope of the invention as originally disclosed in the specification.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
May 23, 2005